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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,431	04/05/2004	Mechthild Rieping	7909/84003	1565

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EXAMINER

CHOWDHURY, IQBAL HOSSAIN

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/817,431	Applicant(s) RIEPING ET AL.	
	Examiner Iqbal Chowdhury, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 March 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 and 15-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 15-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/04, 10/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is an US application filed on 4/5/2004.

The preliminary amendment filed on 3/8/2006 amending claims 1, 3-9, 11-12 and 15-17 and canceling claims 13, 14 and 18-20 is acknowledged. Claims 1-12, and 15-17 are pending.

Applicant's election without traverse of Group I, Claims 1-10, 11-12 and 15-17, drawn to a process for the production of an L-amino acid product by fermentation comprising a microorganism wherein the yfiD ORF gene are over expressed and in addition one or more additional genes are enhanced and thrABC operon as species in the response filed on 3/8/2006 is acknowledged.

Claims 1-12, and 15-17 are at issue and are present for examination.

Priority

Acknowledgement is made of applicants claim for foreign priority of DE 10316109.0 of 4/9/2003.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: ---Enterobacteriaceae strains over-expressing yfiD gene for the fermentative production of L-threonine---.

Claim Objections

Claim 1 is objected to because of the recitation “an L-amino acid product” should be “an L-amino acid”. Appropriate correction is required.

Claims 1, 3-9, and 11-12 are objected to because of the recitation “yfiD”, as abbreviations should not be used without at least once fully setting forth what they are used for. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a process for the production of an L-amino acid by fermentation comprising culturing a microorganism of Enterobacteriaceae family in which a genus of DNA molecule encoding any yfiD polypeptide is over-expressed. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with

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a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Claims 3-6 recite that the recombinant microorganism is made by transforming with a vector comprising yfiD gene and number of copies of yfiD gene is increased by at least 1 either by integration or by extra-chromosomally replicating vector. Claims 7 and 8 recite that the over-expression of the said yfiD gene is achieved by 1) mutating the promoter or ribosomal binding site; or 2) incorporating an expression cassette or promoter upstream of said yfiD gene. Claims 11 and 12 recite that the recombinant microorganism is over-expressing at least one gene of the recited L-amino acid biosynthesis pathway such as thrABC operon in addition to yfiD gene. The specification teaches the structure of only one representative species of such yfiD genes and fails to teach any mutations to the promoter of said genes which result in increased expression of the gene. Moreover, the specification fails to describe any other representative species of yfiD gene by sufficient identifying characteristics or properties as well as how to mutate the promoter or ribosomal binding sites upstream to any yfiD gene to increase the expression of yfiD protein to show that applicant was in possession of the claimed genus with identifying characteristics. Thus for the reasons discussed, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-12 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for the production of L-threonine by fermentation comprising culturing a recombinant *E. coli* wherein the *yfiD* gene of *E. coli* K12 MG1655 and *thrABC* operon are enhanced by increased expression due to introduction of heterologous *trc* promoter or due to increased copy number, does not reasonably provide enablement for a process for the production of any L-amino acid by fermentation comprising culturing any Enterobacteriaceae comprising any *yfiD* gene or any gene of the L-amino acid biosynthesis pathway is over-expressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-12 and 15-17 are so broad as to encompass a process for the production of an L-amino acid by fermentation comprising culturing any Enterobacteriaceae wherein any *yfiD* gene or any gene of L-amino acid biosynthesis pathway is over-expressed. Claims 3-6 recite that the recombinant microorganism is made by transforming with a vector comprising *yfiD* gene and number of copies of *yfiD* gene is increased by at least 1 either by integration or by extra-chromosomally replicating vector. Claims 7 and 8 recite that the over-expression of the said gene is achieved by 1) mutating the promoter or ribosomal binding site; or 2) incorporating an expression cassette or promoter upstream of said *yfiD* gene. Claims 11 and 12 recite that the recombinant microorganism is over-expressing at least one gene of the recited L-amino acid biosynthesis pathway such as *thrABC* operon in addition to *yfiD* gene.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of genes broadly encompassed by the

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claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one yfiD gene of E. coli K12 MG1655 and several genes of L-amino acid biosynthesis pathway.

The scope of the claims is also not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods, which can be used for mutating the promoter sequence or ribosome binding sites, for over-expression of the said yfiD gene products broadly encompassed by the claims. Since the promoter sequence or ribosome binding site of a protein determines its expression, predictability of which changes can be tolerated in a promoter sequence or ribosomal binding site sequence and obtain the desired activity requires a knowledge of and guidance with regard to which nucleotide residues in the protein's promoter sequence or sequence of ribosome binding site, if any, are tolerant of modification and detailed knowledge of the ways in which the proteins' promoter sequence or ribosome binding site sequence structure relates to its expression. However, in this case the disclosure is limited to the only replacement of the promoter region with an inducible trc promoter to achieve over-expression of the yfiD gene encoding protein for increased threonine biosynthesis.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims,

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and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass a method of making any amino acid by over-expressing in any microorganism any yfiD gene or any gene of L-amino acid biosynthesis pathway because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting yfiD polypeptide activity and activity of any other genes encoding polypeptides of L-amino acid biosynthesis pathway; (B) the general tolerance of yfiD polypeptide and other polypeptides of L-amino acid biosynthesis pathway to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any yfiD residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The specification does not support the broad scope of the claims which encompass a method of making any amino acid by over-expressing in any microorganism any yfiD gene by using any method for mutating the promoter sequence or ribosomal binding sites because the specification does **not** establish: (A) regions of the promoter or ribosome binding site which may be modified with over-expression of yfiD polypeptide activity; (B) the general tolerance of promoter region or ribosome binding sequence of yfiD gene to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any promoter sequence or

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ribosome binding sequence of yfiD gene with an expectation of obtaining the desired expression and function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of using any yfiD gene and any methods for modification of its promoter or ribosome binding sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any yfiD gene, its promoter activity and any other genes encoding polypeptides of L-amino acid biosynthesis pathway to use in the claimed methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

Status of the claims:

Claims 1-12 and 15-17 are pending.

Claims 1-12 and 15-17 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

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